REMARKS

Claims 1-3, 5, 6, 14, 15 and 41 are pending in the application.

Claims 2, 4, 7-13, 16-40, and 42-67 are cancelled without prejudice.

Claims 1, 3, 5, 6, and 41 are amended.

I. Amended Claims 1, 3, 5, 6, and 41

Claim 1 is amended to encompass only articles of manufacture that comprise pharmaceutical compositions consisting essentially of at least about 0.1 weight percent an active Raf protein in a physiologically tolerable excipient or carrier. The term "isolated" which was added in the previous amendment is deleted, as is the Markush group directed to inactive Raf proteins. Support for this amendment is found in the specification at page 35, line1, through page 36, line 7.

Claims 3, 5 and 6 are amended to change the dependency from cancelled claim 2 to claim 1, from which cancelled claim 2 depended.

Claim 41 is amended to limit the claim to compositions containing at least about 0.1 weight percent of specific active Raf proteins in a physiologically tolerable excipient or carrier. Support for this amendment is found in the specification at page 35, line1, through page 36, line 7.

No new matter is added by any of the aforementioned amendments.

II. Objections to the Claims

The Markush group in claim 1 directed to active and inactive Raf proteins was objected to as being improper because active and inactive Raf proteins have difference functions and difference structures. Claim 1 is amended herein to limit the claim to active Raf proteins.

III. Rejections Under 35 U.S.C. §112, First Paragraph.

Claims 1 and 41, and claims depending therefrom, have been rejected under the first paragraph of 35 U.S.C. §112, because the term "isolated" added to claims 1 and 41 in the previous amendments allegedly introduced new matter. Applicants believe the term "isolated' is inherent in the written description of the present invention, however, in the interest of advancing prosecution, the term "isolated" is deleted from claims 1 and 41 by the present amendments.

IV. Claim 41 is Not Anticipated by Freed *et al.*

Claims 41 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Freed *et al.*

Freed *et al.* is directed to complexes of Raf-1 and human 14-3-3 proteins and to methods for identifying novel drugs which modulate Raf activity *in vivo* (see Abstract and claims). Freed *et al.* discloses the structure of Raf-1 protein and various fragments thereof and interactions between these proteins and human 14-3-3 proteins. Freed *et al.* do not teach or suggest that the specific active Raf proteins (c-Raf, a protein having the amino acid sequence corresponding to residues 306 through 648 of SEQ ID NO: 2, and Raf-caax) set forth in the claim can stimulate angiogenesis. Nor does the reference teach or suggest a pharmaceutical composition *consisting essentially of at least about 0.1 weight percent* of the specified active Raf proteins in a physiologically tolerable excipient or carrier, as required by presently amended claim 41. The reference is directed to complexes of Raf proteins and 14-3-3 proteins. The "consisting essentially of" language of the claim excludes the 14-3-3 proteins that are essential to the complexes of Freed *et al.* Accordingly, this reference cannot anticipate claim 41, since it does not teach or suggest all of the limitations of the claim.

V. Claim 41 is Not Anticipated by Chow *et al.*

Claim 41 stands rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Chow *et al.*

Chow *et al.* is directed to functional mapping of the N-terminal regulatory domain of human Raf-1 (see Title and Abstract). This reference discloses Raf-1 and various internal deletion variants of Raf-1 and presents scientific studies aimed at determining the function off various regions of the Raf-1 protein. Chow *et al.* do not teach or suggest that the specific active

Raf proteins (c-Raf, a protein having the amino acid sequence corresponding to residues 306 through 648 of SEQ ID NO: 2, and Raf-caax) set forth in claim 41 can stimulate angiogenesis. Nor does the reference teach or suggest a pharmaceutical composition *consisting essentially of at least about 0.1 weight percent* of the specified active Raf proteins in a physiologically tolerable excipient or carrier, as required by presently amended claim 41. There is no mention of pharmaceutical compositions of Raf proteins in this reference, much less of compositions having the specified concentration of Raf protein. Chow *et al.* cannot anticipate claim 41, since the reference does not teach or suggest all of the limitations of the claim.

VI. Claims 1, 3, 5, 6, 14, 15 and 41 are Not Obvious over Freed *et al.*, Chow *et al.* or Any Combination Thereof.

Claims 1, 3, 5, 6, 14, 15 and 41 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Freed *et al.* In a separate rejection these same claims were deemed obvious over Chow *et al.* The present claims are not obvious in view of either reference alone, nor in view of these references in combination. In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). That is not the case here. Additionally, "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970).

The teachings for Freed *et al.* and Chow *et al.* were discussed above. Claim 1 is directed to an article of manufacture comprising a packaged pharmaceutical composition. The composition consists essentially of at least about 0.1 weight percent of a specific active Raf protein in a physiologically tolerable excipient or carrier. The packaging material bears a label with specific instructions and directions setting forth how the composition is used. As noted above, neither reference teaches or suggests the pharmaceutical composition set forth in the claim. Nor does either reference teach or suggest the use of such compositions to stimulate angiogenesis, as set forth in the label limitation of the claim. The Office Action states that printed word on a label cannot be given patentable weight. Applicants respectfully submit that this is incorrect. See *In re Miller*, 164 USPQ 46, 49 (CCPA 1969):

> "... printed matter, in an article of manufacture claims, can be given patentable weight ... no attempt is here being made to patent printed matter as such. The fact that printed matter by itself is not patentable subject matter, because non-statutory, is no reason for ignoring it when the claim is directed to a combination ... The solicitor seems to urge that we ignore the claim limitations to the legends because they are printed and because printed matter is not patentable subject matter by itself ... we reject that argument."

In claim 1, the printed matter on the label should be given patentable weight because the instructions and information on the label impart functionality to the composition. The printed matter distinguishes this article of manufacture from other articles containing such a composition. Furthermore, the information on the label *vis-a-vis* the ability of active Raf proteins to stimulate angiogenesis, is novel, and informs the user of the article how the article is to be utilized. This label limitation is analogous to the situation in *Miller* where the item at issue was a measuring cup. Without the printed matter, the cup had a utility of its own. With the printed matter, the measuring cup had a new and distinct utility (facilitating the preparation of fractional portions of a recipe without the need for mathematical calculations). The printed matter was specifically claimed to be "on" the cup, and this sufficed to provide the structural relationship necessary to carry out the invention.

Similarly, *In re Gulack*, 217 U.S.P.Q. 401, 403 (C.C.P.A. 1983) involved a band imprinted with a series of digits derived from a mathematical algorithm. The band could be a hat band, for example, having utility on its own. The printed matter on the band conveyed a new utility to the band, i.e., it was now useful for performing "magic tricks" and for displaying various aspects of number theory. The CCPA found that the band supported the numbers and the numbers had a relationship to each other that provided a new utility to the band.

Neither Freed *et al.* nor Chow *et al.* teach or suggest the label limitation of claim 1. Neither reference teaches or suggests the composition consisting essentially of at least about 0.1 weight percent of an active Raf protein in a physiologically tolerable excipient or carrier. There is nothing in the references that would have lead one of ordinary skill in the art at the time the application was filed to obtain the claimed article. Even if the teachings of the references

were combined, such a combination does not correct the defects of the individual references. The combination does not teach or suggest all limitations of the claim, which is a material requirement for obviousness. These references do not render claim 1 obvious, either alone or in combination. The dependent claims are also non-obvious in view of the applied references, since these claims include all of the limitations of claim 1 which are missing from the references. Similarly, claim 41 is non-obvious in view of the applied references, as well. The references, alone and in combination, do not teach or suggest all of the limitations of the claim.

VII. Conclusion

Claims 1, 3, 5, 6, 14, 15, and 41 meet all of the requirements of 35 U.S.C. §112 and are patentable over the applied art. Reconsideration of the final rejection and early passing of this application to issue is earnestly solicited. In the event that the Examiner does not consider the foregoing to be persuasive, Applicants request that the present Amendment be entered to place the claims in better form for appeal.

Respectfully submitted,

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